German Cardiac Society Working Group on Cellular Electrophysiology state-of-the-art paper

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German Cardiac Society Working Group on Cellular Electrophysiology State of the Art Paper:

Impact of Molecular Mechanisms on Clinical Arrhythmia Management

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Abstract

Cardiac arrhythmias remain common challenges and are associated with significant morbidity and mortality. Effective and safe rhythm control strategies are a primary, yet unmet need in everyday clinical practice. Despite significant pharmacological and technological advances, including catheter ablation and device-based therapies, the development of more effective alternatives is of significant interest to increase quality of life and reduce symptom burden, hospitalizations and mortality. The mechanistic understanding of pathophysiological pathways underlying cardiac arrhythmias has advanced profoundly, opening up novel avenues for mechanism-based therapeutic approaches. Current management of arrhythmias, however, is primarily guided by clinical and demographic characteristics of patient groups as opposed to individual, patient-specific mechanisms and pheno-/genotyping. With this State-of-the-Art paper, the Working Group on Cellular Electrophysiology of the German Cardiac Society aims to close the gap between advanced molecular understanding and clinical decision making in cardiac electrophysiology. The significance of cellular electrophysiological findings for clinical arrhythmia management constitutes the main focus of this document. Clinically relevant knowledge of pathophysiological pathways of arrhythmias and cellular mechanisms of antiarrhythmic interventions are summarized. Furthermore, the specific molecular background for the initiation and perpetuation of atrial and ventricular arrhythmias and mechanism-based strategies for therapeutic interventions are highlighted. Current “hot topics” in atrial fibrillation are critically appraised. Finally, the establishment and support of cellular and translational electrophysiology programs in clinical rhythmology departments is called for to improve basic-science-guided patient management.

Keywords: antiarrhythmic therapy; arrhythmogenesis; cellular electrophysiology; ion channels; pathophysiology

Introduction

Cardiac arrhythmias remain a clinical challenge and source of morbidity and mortality in developed countries [1]. Research into molecular mechanisms of arrhythmias began more than 40 years ago with the discovery of the cellular mechanisms of delayed afterdepolarization-induced triggered activity and the mechanisms of reentry [2]. Since then, there has been great progress in the understanding of the molecular basis of arrhythmias, fueled by technological advances and new experimental methods ranging from cellular electrophysiology, genetics and genomics to high resolution microscopy.

In parallel, there have been amazing developments in treatment options with significant pharmacological and technological advances, including catheter ablation and device-based therapies [3-8]. However, progress has been largely based on empirical rather than targeted mechanism-based approaches. The rapid progress in device and ablation therapies compared to the relatively poor outcomes of pharmacological rhythm control treatment may have reduced the interaction between clinical electrophysiologists - whose primary interest is improving the health and quality of life of patients - and basic electrophysiologists, who are driven by novel scientific discoveries, which may take years to reach the clinical setting [2].

This state of the art paper summarizes the current knowledge about basic cellular electrophysiology and its clinical implications. We will highlight examples where basic cellular electrophysiology has contributed to the development of novel translational therapeutic strategies. Finally, we will emphasize the importance and advantage of a close interaction between clinical and basic electrophysiologists, in order to solve current and future challenges in cardiac arrhythmia management [1].

Fundamental mechanisms of cardiac arrhythmias

Pronounced heterogeneities exist in mechanisms, presentation, treatment and outcome, between different cardiac arrhythmias and between patients with the same type of arrhythmia. Nonetheless, basic research has identified several important fundamental mechanisms of cardiac arrhythmogenesis [9]. In particular, arrhythmias require a vulnerable substrate characterized by structural or electrical abnormalities and an acute initiating event. Both components can be genetic or, more commonly, acquired due to advancing age or concomitant cardiovascular risk factors and can promote abnormal impulse formation (ectopic activity) and/or abnormal impulse conduction (resulting in reentrant activity), which are considered the major fundamental arrhythmia mechanisms.

Ectopic activity and reentry

Ectopic activity is the local generation of action potentials (APs) outside the normal activation sequence, which can serve as an initiator of reentry-mediated arrhythmias or maintain the fibrillatory process when occurring repetitively at high frequency. Polymorphic ventricular tachycardia (VT) or ventricular fibrillation often originate from the Purkinje system, which is characterized by distinctive electrophysiological characteristics promoting the generation of ectopic excitations and which can be targeted by catheter ablation [10]. In addition, ectopic excitations may trigger premature ventricular contractions, which worsen myocardial function and contribute to increased mortality in patients with structural heart disease [11]. Mechanistically, ectopic activity results from abnormal automaticity or triggered activity resulting from early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs) [12]. Abnormal automaticity, i.e., spontaneous AP generation from normally quiescent tissue, is often mediated by a reduction in ion currents that stabilize the resting membrane potential (RMP; e.g., the basal inward-rectifier potassium current, I_{K1}) or an increased activity of hyperpolarization-activated pacemaker channels responsible for the funny current, I_f. On the other hand, EADs typically result from excessive AP duration (APD), providing time for

reactivation of L-type calcium channels. Finally, DADs result from calcium-handling abnormalities, whereby spontaneous calcium-release events from the sarcoplasmic reticulum (SR) through so-called ryanodine receptor type-2 (RyR2) channels activate a transient-inward current, mediated largely by the sodium/calcium-exchanger (NCX), which depolarizes RMP and can trigger a new AP. An increased incidence of spontaneous calcium-release events can be due to RyR2 dysfunction or due to increased SR calcium load. A classical example for the latter are arrhythmias induced by cardiac glycoside intoxication, where inhibition of sodium-potassium-ATPase increases the intracellular sodium-concentration. This leads to increased cytosolic calcium by reducing the driving force of calcium efflux via NCX at resting membrane potential and favoring reverse-mode NCX-mediated calcium-entry during the AP. The resulting increased SR calcium load explains the positive inotropic effect of cardiac glycosides but also favours spontaneous calcium releases and DADs [13,14].

Reentry is considered the primary arrhythmia-maintaining mechanism [15]. Conceptually, reentry describes a stable circulating excitation. Reentry can occur around an anatomically defined inexcitable core when the product of effective refractory period (ERP) and conduction velocity (the so-called wavelength) is sufficiently small, allowing the tissue to become re-excitable before the reentering impulse arrives. As such, structural remodeling, particularly fibrosis, strongly promotes reentry. Reentry may also occur on a purly functional basis. The classical “leading-circle” concept, describes reentry around a continuously refractory core with a circuit size equal to the wavelength [15]. However, the notion that sodium-channel blocking agents are effective in cardioversion of atrial fibrillation (AF) challenged this concept, since conduction slowing is supposed to stabilize reentry acording to the “leading-circle” concept rather than suppressing it. Based on this paradox the “spiral wave” concept has been developed, wherein reentry proceeds around an excitable but continuously unexcited center and maintenance of reentry depends on the balance between the

wavefront's excitatory currents (the 'source') and the properties of the unexcited tissue (the 'sink') [16-18] .

Spiral wave reentry, often visualized as rotors, represents a major pathophysiological concept in AF and rotor ablation has been suggested as potential ablation strategy of persistent AF [19,20], which is presently evaluated in various clinical trials (ClinicalTrials.gov numbers: NCT02101541, NCT02274857, NCT01924377, NCT02386345, NCT02497248, NCT02113761).

Slow conduction

Cardiac fibrosis is a hallmark of structural remodeling, promoting slow, heterogeneous conduction and spatial dispersion of repolarization by isolating muscle-bundles. Advances in clinical imaging methodologies have helped to establish the important role of fibrosis in arrhythmogenesis [12]. In parallel, basic science has identified the mechanisms underlying the proliferation of fibroblasts and their differentiation into myofibroblasts, which is a central response to numerous stress signals activated in many cardiovascular diseases, resulting in excessive collagen production and fibrosis [21]. Experimental models have identified the major underlying signaling pathways and have indicated that targeting these pathways, either using clinically approved drugs (e.g., angiotensin-converting enzyme inhibitors, aldestorone antagonists) or through new targets (e.g., microRNAs such as miR-21 or miR-29) may limit the development of a proarrhythmic substrate [21]. However, there is increasing awareness that such therapy would need to be applied early in the disease process, before extensive fibrosis is already present. Other observations suggest that fibrosis and structural alteration can be partly reversible, if the underlying condition is effectively treated.

Reentry-promoting slow conduction is also mediated by gap-junction remodeling, resulting in impaired electrical cell-to-cell coupling. Preclinical studies have shown that the expression of connexin-43, the predominant constituent of ventricular gap-junction channels, is reduced

under pathological conditions (e.g., post-myocardial infarction), contributing to slowed conduction, and that gene transfer of connexin-43 reduces the inducibility of ventricular tachycardia in pigs, providing an important proof-of-concept for the antiarrhythmic effects of targeting the mechanisms underlying slow conduction [22].

Alternans

Cardiac alternans is evident on the surface ECG as beat-to-beat alternations in the ST segment or the T-wave. At the cellular level, APD alternans underlies T-wave alternans (TWA) in the surface ECG. When APD alternans becomes spatially discordant, a small reduction of cycle length may result in unidirectional block followed by reentry and initiation of ventricular fibrillation thus providing a mechanistic link between TWA and sudden cardiac death (SCD) [23]. Basic science has revealed that cardiac alternans is often caused by perturbed cellular calcium signaling [24]. In support of this notion, normalization of SR calcium handling in animal models of heart failure (HF) reduced the incidence of cardiac alternans and ventricular arrhythmias [25]. Thus, normalization of RyR2 function and SR calcium handling may be promising targets to prevent development of alternans and SCD.

Inherited channelopathies

Inherited channelopathies are the prime examples of cardiac diseases in which basic science has provided important mechanistic understanding of the pathophysiology. This has led 1) to the development of specific diagnostic tests such as ajmaline challenge in Brugada syndrome [26], QTc evaluation during stress test in long and short QT syndromes (LQTS, SQTS), and importantly 2) to the continued exploration and development of mechanism-based therapeutic approaches such as late sodium channel block in LQT3 [27] and the use of flecainide in catecholaminergic polymorphic ventricular tachycardia (CPVT) [28] that have already partially entered the clinical guidelines [29].

Long and short QT syndrome

Both, pathological prolongation (LQTS) and acceleration (SQTS) of cardiac repolarization can predispose patients to atrial and ventricular tachycardia (AT/VT) and SCD [29]. Since the link of mutations in *KCNQ1* and *KCNH2/HERG* potassium channel and *SCN5A* sodium channel genes to inherited LQTS was established in the 1990s [30,31], mutations in 15 genes have been linked to LQTS and mutations in 6 genes to SQTS [29]. An increased understanding of the biophysical consequences of these mutations (complete loss-of-function vs. change in voltage-dependence of the respective currents) and the exact location of the mutation within the channel (pore-region vs. C- and N-terminus) may have clinical relevance for risk prediction [32,33].

Characterization of the biophysical properties of the mutated channels and their response to sympathetic activity has helped to identify the importance of EADs and sympathetic stimulation as proarrhythmic triggers, providing the scientific basis for beta-blocker therapy (or left cardiac sympathetic denervation) as mainstay of antiarrhythmic therapy in LQTS [29].

The subsequent generation of genetic (knock-out/knock-in) and transgenic (mouse and rabbit) models of LQTS has provided important insights into the major role of spatial and

temporal APD heterogeneities as arrhythmogenic substrate [34]. Mechanisms underlying genotype-specific differences in arrhythmia initiation (sustained sympathetic activity (sports), LQT1; sudden sympathetic activation (startle), LQT2) [35] contributing to the clinically observed genotype-difference in the efficacy of beta-blocker therapy [36] have been identified. The detrimental role of bradycardia and short-long-short sequences as triggers for VTs has been observed in patients and confirmed in (animal) models [27,37]. In addition, the potential of genotype-specific therapeutic approaches has been explored: In genetic murine LQT3 models, with pathologically enhanced late I_{Na}, sodium-channel blockers mexiletine, flecainide, and the more selective GS967 exert a mechanism-directed, genotype-specific antiarrhythmic effect [38-40].Similarly, recent clinical data demonstrate that LQT3 patients benefit from QT-shortening and anti-arrhythmic effects of sodium channel blockers mexiletine, flecainide, ranolazine, and eleclazine [41-46]. The 2015 ESC guidelines for the prevention of SCD thus mention sodium-channel blockers as a potential add-on therapy in patients with LQT3 [47]. Moreover, proarrhythmic effects of estradiol due to increased APD heterogeneities and EADs has been revealed in transgenic LQT2 rabbit models, contrasting with anti-arrhythmic, protective effects of progesterone due to shortening of cardiac refractoriness and reduced EAD formation [48]. These data suggest progesterone-based therapies might constitute novel antiarrhythmic approaches in female LQTS patients.

Recent clinical and basic science data suggest subclinical mechanical dysfunction in the "electrical" disease LQTS due to close electro-mechanical coupling [49] and a correlation between the extent of mechanical dysfunction and arrhythmic risk, strongly suggesting that assessment of regional mechanical dysfunction may be helpful to improve future clinical risk stratification [50].

In SQTS, mechanisms of arrhythmogenesis are less well-understood than in LQTS and therefore effective antiarrhythmic treatment options are sparse. The recent development of genetic/transgenic animal models of SQTS (zebrafish, rabbit) have the potential to close this

gap and help to develop mechanism-based antiarrhythmic therapeutic approaches [Odening et al., submitted 2017].

Brugada syndrome

Brugada syndrome (BrS) is characterized by typical precordial ST-segment elevations on the surface ECG and an increased risk for SCD caused by ventricular arrhythmia [51]. The identification of SCN5A as important disease gene [52] in BrS suggested that the syndrome was a monogenetic disorder, similar to LQTS. “Loss-of-function” mutations in other genes, implicated in cardiac sodium (GPD1L, SCN1B, SCN3B) or calcium (CACNA1C, CACNB2) channel expression were associated with BrS, as well. “Gain-of-function” mutations in KCND3, by contrast, demonstrated an involvement of increased transient potassium outward current I_{to}, in the pathogenesis of BrS [53,54]. Interestingly, recent data suggested SCN10A and its gene product Nav1.8, primarily expressed in the nervous system and only to a minor extent in the heart, as an important disease gene in BrS [55,56], although another study did not confirm this view [57]. However, only ~30% of cases may be explained by the 22 disease–associated genes known so far, pointing to a multifactorial origin of the disorder. This view was fueled by recent findings that hearts of BrS patients often show subtle structural changes, in particular in the right ventricular outflow tract (RVOT), suggesting a distinct cardiomyopathy [58]. This is pathophysiologically important as such regions - either caused by channelopathy or even more complex mechanisms - may give rise to areas of low voltage and electrical zig-zag conduction that constitute a substrate for microreentry as arrhythmogenic basis of the syndrome. Observations in BrS patients undergoing electrophysiological study and reports of successful radiofrequency ablation of critical areas in the RVOT [59], further substantiated this pathomechanistic idea, building the backbone of the depolarization hypothesis. Accordingly, localized slow conduction in the RVOT constitutes the origin of typical ECG changes in right precordial leads.

The repolarization hypothesis, by contrast, postulates an imbalance of ion currents during phase 1 of the right ventricular epicardial AP, mediated by transmural differences in the outward potassium current I_{to} and genetic or drug-induced reduction of I_{Na}, underlying the ECG pattern and the induction of arrhythmias in BrS [60].

Regardless which of the two hypotheses more precisely reflects the underlying mechanisms, it is an important achievement of basic electrophysiological research that a mismatch of depolarizing current (in particular I_{Na}) and I_{to} as well as distinct phases of bradycardia, are major drivers of arrhythmogenicity in BrS. Therefore, modulation of the I_{Na}/I_{to} relation has an important role in current clinical diagnostic, risk stratification and therapeutic approaches in BrS, including (1) the application of sodium current blockers as diagnostic test for inducibility of Brugada ECG (ajmaline or flecainide challenge) [26], (2) the use of quinidine to decrease arrhythmic burden in BrS patients by inhibiting I_{to} [61], (3) the use of isoproterenol or other β-adrenergic stimuli in arrhythmogenic storm to increase depolarizing current (in particular L-type calcium current; $I_{Ca,L}$) and avoid bradycardia [61], (4) avoidance of drugs that decrease I_{Na} or increase I_{to} (see www.brugadadrugs.org) and (5) avoidance of fever to prevent temperature-induced I_{Na}/I_{to} mismatch [62]. However, currently, the only way to safely prevent SCD is the implantation of an implantable cardioverter defibrillator (ICD), indicating an urgent need for basic and translational research to provide better mechanism-based diagnostic and therapeutic strategies.

Catecholaminergic polymorphic ventricular tachycardia

CPVT is a highly lethal inherited arrhythmogenic disorder characterized by episodes of polymorphic VT and SCD in the setting of exercise or emotional stress. In recent years significant progress has been made to understand the underlying mechanisms, which has positively impacted the therapy of CPVT patients [63]. The molecular basis of CPVT has mostly been attributed to dysfunction of the RyR2 channel, promoting calcium-handling

abnormalities, DADs and triggered activity, particularly during increased sympathetic tone when SR calcium load increases and RyR2 channels become hyperphosphorylated, further promoting their dysfunction [64]. In ≈ 65% of CPVT patients, this RyR2 dysfunction is due to mutations in the *RYR2* gene itself (CPVT1), but mutations in proteins regulating RyR2 function as part of the macromolecular complex that controls SR calcium release (e.g., calsequestrin-2 or calmodulin), which can indirectly promote RyR2 dysfunction, have also been described [64,63].

Recent data from animal models of CPVT suggest that the primary defects in calcium handling may also cause sinoatrial node (SAN) dysfunction, fibrosis, atrial arrhythmias, exaggerated left ventricular (LV) hypertrophy and HF [65]. These findings may explain why some affected patients exhibit bradycardia and atrial arrhythmias, in addition to CPVT. Moreover, they provide a direct mechanistic link between a primary calcium handling disease and structural remodeling in the heart. This might have more widespread implications for other diseases.

The identification of the underlying arrhythmogenic mechanisms has played an important role in the treatment of CPVT patients, which involve inhibition of sympathetic activity (beta-blockers or left cardiac sympathetic denervation) and the use of flecainide. The role of flecainide in CPVT represents a prime example of the interaction between basic scientists and clinicians. It was initially established in mice and applied as a proof of concept in two CPVT patients [28], but has since then become a class IIa guideline recommendation [29]. However, the exact antiarrhythmic mechanism of flecainide remains a topic of debate and may involve a combination of sodium channel block (preventing triggered activity), inhibition of RyR2 (reducing the likelihood of spontaneous SR calcium-release events), or indirect effects on intracellular calcium handling due to changes in intracellular sodium [66,67]. Based on the underlying mechanisms of CPVT, RyR2 dysfunction is considered a promising therapeutic target. Several RyR2-stabilizing compounds, including K201/JTV-519, S107 and

carvedilol-analogues, have indeed shown promise in preclinical studies [68]. Of particular clinical interest are the effects of dantrolene, an RyR-stabilizing drug approved for the treatment of malignant hyperthermia, which also has antiarrhythmic effects in CPVT patients [69,70].

Electrical conduction defects

Cardiac conduction defect (CCD) also comprises primary genetic forms, although most cases arise from age-related fibrotic degeneration of the conduction system. The yield of genetic testing in CCD is ~30 % [71]. Isolated CCD can be caused by mutations in *SCN5A* (progressive familial heart block 1a) [72] or *TRPM4* (progressive familial heart block 1b) [73]. In association with cardiomyopathy, CCD was linked to *LMNA* [74] and *PRKAG2* mutations [75]. Patients with such mutations are also at risk of ventricular arrhythmias rendering further decision making regarding ICD implementation important. Furthermore, mutations in *NKX2-5* [76] and *TBX5* [77] cause CCD in association with congenital heart disease. Thus, evidence for genetic forms of CCD can significantly improve stratification of patients, as it constitutes a prognostic indicator for the course of disease with or without a syndromic co-morbidity.

Hereditary sinus node disease

Loss or dysfunction of SAN cells results in sinus node disease (SND), comprising sinus bradycardia, SAN block or arrest and bradycardia-tachycardia syndrome (BTS) [78]. In the majority of cases SND is “idiopathic” and occurs age-dependently either by cellular dysfunction of SAN cells or degeneration of the formerly intact SAN.

Loss-of-function mutations in *SCN5A* are an established pathomechanism (sick sinus syndrome 1). Electrophysiological studies and computational modeling established that mutated channels cause either abnormally slow pacemaking or produce SAN exit block [78]. Furthermore, mutations in *HCN4* underlying a significant proportion of the pacemaker current I_f in the SAN, cause hereditary SND (sick sinus syndrome 2) and BTS, respectively [79-81].

HCN4 gain-of-function mutations are associated with inappropriate sinus tachycardia. Functional investigations showed that *HCN4*-R524Q mutant channels, heterozygously carried by affected family members, have an increased cAMP sensitivity resulting in an augmented funny-current at baseline leading to a faster resting heart rate [82]. Thus, inappropriate sinus tachycardia in part has a genetic basis, which raises the possibility of inheritable traits.

Importantly, investigation of I_f and its underlying ion channels, built the groundwork for ivabradine, the first clinically available I_f blocker targeting impulse formation in the SAN. This pharmacological mechanism is successfully used to treat patients with chronic stable angina and HF [83].

Drug-induced, reversible “channelopathies”

Various drugs can phenocopy ECG features and arrhythmias of genetic channelopathies by interacting with different cardiac ion channels, causing for example acquired LQTS and BrS - particularly in patients harboring single-nucleotide polymorphism variants or even silent disease-causing mutations [84]. Most drugs causing acquired LQTS block HERG-encoded I_{Kr} [85]. However, drugs may also cause acquired LQTS by blocking other currents such as I_{Ks} (e.g., isoflurane) or I_{K1} (e.g., midazolam) [86]. Drug-induced BrS is often caused by sodium-channel-blocking class 1 drugs [84]. Overall, acquired drug-induced “channelopathies” and arrhythmias are much more prevalent than rare genetic forms and exploring their mechanisms has important pre-clinical and clinical implications to prevent adverse drug effects.

Safety pharmacology

Every new pharmacological agent under development undergoes extensive cardiac safety testing to exclude any proarrhythmic liability [85]. Until recently, cardiac safety assays predominantly involved high-throughput screening of HERG blockade early on and a so-called ‘thorough QT study’ assessing repolarization prolongation in humans later on in drug development. However, extensive basic science studies have established that HERG screening alone has limited sensitivity and specificity to identify proarrhythmic compounds, which has prompted a more integrative approach to assess the cardiac safety of new compounds. The Comprehensive In vitro Proarrhythmia Assay (CIPA) initiative [87] advocates the use of 1) screening of ion-channel-blocking effects beyond HERG alone, 2) in silico integration of these findings to assess overall effects on ventricular repolarization and 3) use of integrated biological systems such as induced pluripotent stem cell-derived cardiomyocytes (IPSC-CM).

Ventricular arrhythmia in subjects with structural heart disease

Ventricular arrhythmias remain a major contributor to increased mortality in patients with ischemic or nonischemic cardiomyopathy [47]. Underlying pathophysiology, risk markers and current treatment options are outlined below. Outflow tract tachycardia and idiopathic LV tachycardia are not discussed due to lack of significant basic science data.

Ischemic cardiomyopathy (ICM)

Ischemia results in release of reactive oxygen species, increase in intracellular sodium due to sodium/hydrogen exchange and inhibition of the sodium/potassium-ATPase triggered directly by hypoxia or secondary to ATP depletion. Within hours after ischemia onset, associated cytokine- and chemoattractant-mediated endothelial dysfunction, apoptosis, autophagy, platelet aggregation and micromebolization, and neutrophil accumulation as well as macrophage and T-cell-mediated cell-damage occur [88,89].

While acute ischemia/reperfusion injury primarily leads to ventricular fibrillation, myocardial infarction related regional scars and especially the border zone between infarcted and vital myocardium are an important substrate for VT occurrence in ICM: Infarct related changes in excitability and conduction velocity as arrhythmogenic substrate lead to perpetual reentrant VT (see also Figure 2).

Pharmacological treatment of ventricular fibrillation is currently limited [47]. Class I antiarrhythmic drugs are contraindicated due to increased risk for arrhythmia associated sudden cardiac death as shown in the “Cardiac Arrhythmia Suppression Trial” (CAST) [90].

After the CAST study had abolished the use of Class I antiarrhythmic drugs in ICM, several antiarrhythmic compounds underwent evaluation, as the alternative compound amiodarone besides its antiarrhythmic potential had shown to have cumulative toxicity in many body organs.

Class III antiarrhythmic compound, MS551 (nifekalant), was described to have antiarrhythmic properties shortly after the CAST results had been published [91]. The pyrimidine derivative leads to frequency dependent AP-prolongation. It has voltage- and frequency dependent inhibitory properties on HERG encoded I_{Kr} with high affinity for "open state" of I_{Kr}. As described above, this is known to possibly induce an aquired form of QT-interval prolongation with the risk for fatal polymorphic tachycardias including torsades de pointes. However, different from other class III agents, it also has agonistic/facilitating effects on HERG current [92]. Nifekalant has a high potency for destabilization and early termination of spiral wave reentry and to prevent VT/ventricular fibrillation after acute myocardial infarction. It also improves electrical defibrillation efficacy in this setting [93]. However nifekalant is only approved in Japan for the treatment of life threatening ventricular tachyarrhythmias.

Another class III antiarrhythmic compound, SSR149744C (celivarone), is like amiodarone a benzofuran derivative, however, different from amiodarone it is not iodinated, thus has less organ toxicity [94]. Celivarone has antiadrenergic and angiotensin II antagonistic effects and is a multi ion-channel blocker. Similar to amiodarone it is a weak sodium channel blocker with additional I_{Kr}, I_{Ks}, and I_{K1} blocking properties, but less effective in $I_{K,ACh}$-, $I_{Kv1.5}$-, or $I_{Ca,L}$-blockade [94]. In the ICARIOS-trial, celivarone showed a 46% (non-statistically significant) reduction in VT/-ventricular fibrillation triggered ICD shock therapies, however in the ALPHEE Study, celivarone was not effective for the prevention of ICD interventions or death [95].

To date, according to the European Society of Cardiology (ESC) guidelines, only betablockers (in the non-acute phase of MI) and amiodarone are recommended in ischemia related ventricular fibrillation or VT associated with heart failure [47]. Therefore it seems urgently necessary to search for other treatment options of ischemic cardiomyopathy associated arrhythmias.

A very recent and interesting approach comes from experimental data from a pig animal model that evaluated cardiac remodeling in an ischemia/reperfusion setting with or without administration of class III antiarrhythmic compound dronedarone [96]. In a meticulous transcriptome profiling and combined proteome analysis of post-infarction remodeling the authors found the levels of 879 transcripts in the infarction border zone, 7 transcripts in the myocardial infarction area, as well as 51 proteins in the unaffected left ventricle and 15 proteins in the border zone affected by dronedarone treatment. All findings were supported by disease/function charts and an integrated network established by combined "omics". **Table 1** shows transcriptomics with most predominant changes in gene expression. Besides the fact that dronedarone is not approved for ventricular arrhythmias, this genuine approach highlights the importance of myocardial infarction border zone in ICM. Secondly, it may lead to similar evaluation approaches for future antiarrhythmic compounds that can improve our understanding of arrhythmogenesis on a subcellular transcriptome and proteome level.

Autonomic nervous system

Autonomic imbalance characterized by increased sympathetic activation and parasympathetic withdrawal along with changes in density and spatial distribution of the intrinsic efferent innervation of the ventricles may account for the timing of clinical presentation of arrhythmias after ventricular injury [97]. Sympathetic hyperinnervation in the ventricle occurs post-MI and has been linked to ventricular arrhythmias. Whereas nerve growth factor (NGF) stimulates axon growth, its precursor, proNGF, triggers axon degeneration and may be involved in regional denervation after myocardial injury. Additionally, denervated reperfused infarcts display β-adrenoreceptor supersensitivity [98]. Both sympathetic hyperinnervation and denervation of the ventricles can lead to heterogeneous β-adrenoreceptor activation, either through localized catecholamine release or localized β-adrenoreceptor supersensitivity. This non-uniform sympathetic activation increases the risk of focal triggers and creates gradients of repolarization, increasing the

susceptibility to reentry. Attempts to therapeutically reduce sympathetic activation or sympathetic nerve sprouting (e.g. by cardiac sympathetic denervation or renal denervation) [99-101] or to increase cardiac parasympathetic tone (e.g., by baroreceptor stimulation) [102] reduce arrhythmias in animal models and selected cohorts of patients.

Non-ischemic cardiomyopathy

Non-ischemic cardiomyopathies include genuine dilated or congestive cardiomyopathy (DCM) and special cases such as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

While in ICM usually focal areas with post ischemic/MI fibrosis and scarring can be found that lead to reduced myocardial contractility, in DCM the impaired myocardial contractility is generally dispersed.

Pathophysiology of VT generation in DCM is as complex as its variety of genetic causes. Nowadays, an abundance of genes and alleles that contribute to phenotypic DCM are identified [103]. Gene alterations of TTN (coding for Titin, 12-25% of DCM), LMNA (coding for Lamina/C, 4-8% of DCM), DES, VLC and FLNC (coding for cytoskeletal proteins, each around 1% of DCM) significantly contribute to the DCM phenotype [103]. While DSP, coding for desmoplakin, also contributes to DCM, other desmosome changes instead result in ARVC/M. Loss of RNA-binding protein 20 (RMB20), which is a RNA-binding protein of spliceosome of TTN and calcium/calmodulin-dependent protein kinase II (CaMKII) delta, leads to a clinically aggressive form of DCM [104]. Despite similar left ventricular function, altered calcium handling increased arrhythmic burden (44% vs. 5%) when RBM20 mutation carriers were compared to TTN mutation carriers [104]. Therefore, $I_{Ca,L}$-blockers may possibly reduce arrhythmia burden in this disease entity. Besides playing a role in LQTS3 and BrS, SCN5A mutations also can lead to DCM or ARVC/D [105]. In some cases with a gain-of-function mutation in the sodium channel (i.e. in p.R222Q mutation carriers) Class I

antiarrhythmic agents have been reported to decrease arrhythmogenic burden and improve left ventricular function [105].

In ARVC/D, several desmosomal and non-desmosomal gene mutations have been identified to induce phenotypic disease. Desmosomal genes include plakophilin 2, desmoglein 2, and desmoplakin gene mutations contributing to half of all cases [106]. Non-desmosomal changes include amongst others gene mutations in the RyR2, phospholamban, Lamin A/C, Desmin, Titin and transforming growth factor 2 [106]. Pharmacological treatment options include betablockers in all ARVC/D phenotype patients, as well as sotalol, amiodarone, and mexiletine. In selected patients epicardial ablation may be considered.

Besides antiarrhythmic drugs, experimental data of mouse models have shown reduced structural and electrical remodeling leading to arrhythmia reduction by blockade of the renin-angiotensin-system. The direct renin inhibitor aliskiren was shown to have antiarrhythmic potential by reestablishing normal ventricular conduction velocities due to restoration of connexin 43 expression in a DCM mouse model [107]. Also, the angiotensin II receptor antagonist candesartan was able to partially reverse pro-arrhythmic down-regulation of Kv4.2 (I_{to} channel protein), KChIP2 (auxiliary subunit of Kv4.2), and Kv1.5 (I_{Kur} channel protein) in another DCM mouse model [108].

To date, however, most treatment approaches in DCM are symptomatic or prophylactic and not driven by pathophysiologic understanding of the disease or underlying genetic pathology. Therefore, the main goal for the future is to gain further knowledge about underlying disease pathology on the organ, cellular, and subcellular levels in order to translate this knowledge into mechanism-based therapeutic approaches.

Atrial arrhythmias

Atrial arrhythmias, particularly AF, are the most common cardiac rhythm disorders and are associated with increased rate of stroke, HF and death. Great efforts have been undertaken to understand the underlying arrhythmic mechanisms and improve treatment options. Although there are now many sophisticated therapeutic options available, antiarrhythmic therapy remains unsatisfactory [109]. In contrast, pacemakers are accepted standard therapy for patients with bradycardia. Similarly, patients with accessory-pathway or AV-nodal reentry syndromes, such as Wolff-Parkinson-White syndrome, are usually successfully treated with ablation therapy [110]. A thorough understanding of the molecular mechanisms underlying the latter has had little impact on therapeutic options and these arrhythmias will therefore not be discussed in further detail.

Atrial tachycardia (AT)

ATs are subdivided based on underlying mechanisms into focal tachycardias and macroreentrant tachycardias, also designated as atrial flutter [111]. Focal ATs commonly arise in the absence of preexisting structural heart disease and can occur at any age with no gender preference [112]. The autonomous nervous system likely contributes to the initiation of focal AT, which can be triggered by changes in posture, belching and swallowing. Pathomechanism of focal AT include abnormal automaticity (19 %), triggered activity (25 %) or microreentry (56 %) [113].

Focal AT due to triggered activity are likely mediated by DADs. Focal AT may also be caused by microreentry, which refers to a small reentrant loop which is below the resolution of current mapping systems [111]. Adenosine can be used to distinguish reentry from other mechanisms underlying AT. Adenosine binding to A_1-receptors leads to dissociation of G_i-proteins and to activation of a repolarizing potassium current ($I_{K,ACh}$), due to direct interaction with the G_i-protein $\beta\gamma$-subunit). The resulting stabilization of the RMP terminates focal AT

caused by afterdepolarizations, transiently suppresses AT due to abnormal automaticity, but does not affect AT based on reentry mechanisms [114].

The current knowledge surrounding underlying AT mechanisms is not yet sufficient to guide antiarrhythmic drug choice, but may help to understand why certain treatment options may be effective in some patients while ineffective in others. There is hope that the future development of selective drugs may provide new therapeutic options for mechanism-based therapy of AT [115].

Atrial fibrillation

a. Remodeling; progression of AF

The "atrial fibrillation begets atrial fibrillation" paradigm [116] states that the longer AF persists, the higher the inducibility and stability of AF, i.e. the higher the likelihood that AF will perpetuate. These basic research findings recapitulate the clinical observation that AF is a highly progressive disease [109,117]. The progressive nature of AF is caused by atrial remodeling processes on the cellular and tissue level, and basic research has been instrumental in unravelling these processes [9]. Atrial remodeling comprises electrical, contractile, structural and calcium handling remodeling. Electrical remodeling is characterized by a dramatic reduction in atrial ERP caused by shortening of atrial myocyte APD. The latter is due to altered regulation and expression of ion channels, e.g. reduced $I_{Ca,L}$ and transient outward potassium (I_{to}) current and increased inward rectifier potassium currents and TASK-1 (K_{2P} 3.1) current [118,117,119,120]. Contractile remodeling is caused by multiple mechanisms including impaired calcium handling and dysregulation of the sarcomeres and myofilaments [117]. Prominent features of structural remodeling are atrial dilatation, atrial myocyte hypertrophy and fibrosis, which creates a substrate for AF [117]. Calcium-handling remodeling includes altered expression and/or regulation (e.g. phosphorylation) of L-type calcium channels, NCX, RyR2, SERCA2a or CaMKII [121-123].

Calcium-handling abnormalities 1) contribute to electrical, contractile, structural and intracellular signalling remodeling; 2) may provide both a trigger (e.g. by spontaneous SR calcium release triggering DADs) and a substrate for AF (by contributing to electrical and structural remodeling); and 3) may be both a cause and consequence of AF [123].

There are notable differences in the time course and reversibility of electrical and structural remodeling with important clinical ramifications. Electrical remodeling is an early event starting within hours or days after initiation of AF and is reversible upon restoration of sinus rhythm [116]. Fibrosis (structural remodeling), on the other hand, is a late event [12] and is considered poorly reversible. In patients, the degree of atrial fibrosis correlates with the occurrence of postoperative AF as well as with the persistence and recurrence of AF [124,125]. Thus, a high degree of atrial fibrosis may be regarded a marker of terminally-remodelled atria highly susceptible to AF. These findings on the time course and progression of atrial remodeling may explain the clinical observation that cardioversion and catheter ablation for rhythm control are more successful in younger patients with shorter history of AF and less atrial structural remodeling [109]. They stress the clinical paradigm that, in order to be treated successfully, AF has to be diagnosed early, i.e. before the development of excessive structural remodeling, which may represent a "point of no return" toward sinus rhythm.

Recent evidence from cellular electrophysiology indicates that calcium-handling remodeling exhibits important differences between paroxysmal and chronic AF [122,121]. These findings have important clinical implications: Firstly, they indicate that paroxysmal and chronic AF may be different entities and that (calcium handling) remodeling does not necessarily represent a continuum from paroxysmal to chronic AF, where a certain alteration simply progresses and aggravates over time. Secondly, they suggest that optimal treatment for paroxysmal and chronic AF could differ and, ideally, should be tailored to the individual remodeling processes in a given patient.

The “complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations” has been summarized as “atrial cardiomyopathy” [126].

b. Mechanism-based stratification of AF subtypes: impact of comorbidities

Patient stratification and antiarrhythmic therapy planning relies primarily on symptoms and the duration of AF (i.e., paroxysmal, persistent, long-standing persistent, or permanent) [109]. This classification is limited by a lack of regard for arrhythmia burden, the predominant underlying mechanism of the arrhythmia, or the severity of the atrial substrate. Specifically, the impact of basic scientific findings on AF categorization and therapeutic decision making has been low in the past, despite significant advances in the field [127]. From a cellular electrophysiologist’s perspective, among the most striking differences between AF patients are changes in APD of atrial myocytes. In patients with persistent or permanent AF but without pronounced LV dysfunction, the “classical” mechanism of atrial arrhythmogenesis is observed, characterized by reentry-promoting shortening of atrial APD [118,117,121]. In these patients, inhibition of repolarizing K^+ channels that are expressed in human atrium by class III antiarrhythmic drugs is expected to be particularly effective in suppressing AF. The coexistence of HF with severe LV dysfunction poses a clinically significant therapeutic challenge attributed to a distinct atrial substrate that was recently studied in detail. In affected patients with paroxysmal AF, atrial APs are prolonged [128]. The hypothesis that manipulations to activate potassium currents could exert antiarrhythmic effects in these cases remains to be tested in translational approaches. Of note, HF-associated APD prolongation and APD shortening in chronic forms of AF offset each other, resulting in apparently normal APD in patients with long-standing persistent AF and severe LV dysfunction.

The development and application of methodologies evaluating the extent of atrial remodeling in patients such as electro-anatomic mapping or late gadolinium enhancement magnetic resonance imaging (LGE-MRI), as well as mapping techniques applied during ongoing arrhythmias (e.g., mapping of focal or re-entrant activity) may help to improve arrhythmia characterization and the initiation of individualized treatment of AF patients. In translational research strategies evaluating antiarrhythmic concepts to be applied in patients with paroxysmal AF or following rhythm control by ablation or cardioversion, the use of cells obtained from subjects with persistent or even permanent AF exhibiting different cellular electrophysiological mechanisms constitutes a limitation that requires careful consideration. Cells obtained from specific patient populations targeted by antiarrhythmic interventions (e.g., paroxysmal AF) should be preferred when studying antiarrhythmic concepts.

c. Vagal AF

AF patients with structurally normal hearts tend to show a vagal pattern of AF onset (nocturnal AF, AF during rest or after exercise), while patients with structural heart disease tend to show a sympathetic pattern (AF during daytime or during exercise) [129]. Other studies in “lone” AF patients suggest that AF onset might be associated with a combined symatho-vagal activation rather than with an increase in vagal or sympathetic drive alone [117]. Nocturnal arrhythmias might be triggered by autonomic activation due to sleep disordered breathing like obstructive sleep apnea. During obstructive respiratory events a profound peri-apneic vagal activation [130] followed by combined sympathetic activation at the end of the apnea during the arousal reaction may trigger AF [131]. Additionally, endurance athletes are more likely to develop AF than non-athletes. The type, intensity and amount of sport appears to influence the risk of developing AF and different mechanisms involving increased vagal tone at rest, increased cardiomyocyte-sensitivity to cholinergic stimulation [132], structural atrial remodeling, sinus bradycardia and genetic predisposition

may contribute to AF in athletes [133]. Treatment of sleep apnea or detraining in athletes may reduce AF burden in these patients.

Classical and novel antiarrhythmic drug paradigms

In contrast to the inherited channelopathies, where insights into arrhythmia mechanisms have greatly advanced antiarrhythmic drug therapy, the ICD remains the cornerstone of antiarrhythmic therapy in patients at high risk for ventricular arrhythmias due to acquired conditions [47]. Indeed, with the exception of beta-blockers, antiarrhythmic drugs have not shown a consistent efficacy in the primary management of arrhythmias in this setting, perhaps because currently available antiarrhythmic drugs were mainly identified based on chance observations during clinical studies, without a precise understanding of the molecular mechanisms underlying initiation and maintenance of arrhythmias [115].

The discovery of sodium-channel block as the major mechanism underlying antiarrhythmic effects of quinidine led to the development of class I antiarrhythmic agents such as flecainide and propafenone. Improved understanding of the fundamental biophysical determinants of state-dependent block of sodium channels subsequently led to the subdivision of agents into classes IA, IB and IC by Vaughan Williams [134]. Ranolazine is a multi-channel blocker, primarily inhibiting I_{Kr} and the late component of the cardiac sodium current, which was originally developed as an antianginal drug. Several studies have supported the therapeutic potential of ranolazine for ventricular arrhythmias. However, the large, randomized, double-blind, placebo-controlled Ranolazine Implantable Cardioverter-Defibrillator (RAID) trial in which high-risk ICD patients with ischemic or nonischemic cardiomyopathy were randomly assigned to ranolazine or placebo only found a non-significant 16% reduction in the primary composite outcome of VT/ventricular fibrillation or death. Furthermore, although more selective blockers of the late sodium current, such as eleclazine, showed strong antiarrhythmic effects in animal studies, all subsequent clinical trials (ClinicalTrials.gov numbers: NCT02104583, NCT02291237, NCT02300558) have recently been discontinued .

Besides beta-blockers, amiodarone is most often used due to contraindications for other antiarrhythmic drugs in the presence of advanced structural heart disease, which is common

in this population. The antiarrhythmic effects of amiodarone were also a coincidental discovery during amiodarone use in the therapy of angina. Further investigations revealed that potassium-channel inhibition by amiodarone reduces the likelihood of reentry by prolonging APD and ERP. In addition, amiodarone blocks sodium and calcium channels and inhibits the effects of alpha- and betaadrenoceptors, thereby possessing properties of all four Vaughan Williams classes of antiarrhythmic agents. Therefore combined blockade of multiple ion channels has recently been suggested to underlie the relatively high anti-AF efficacy of amiodarone [135]. However, amiodarone's extracardiac toxicity has motivated the search for alternatives [136]. Dronedarone is the first amiodarone-analog and exhibits reduced toxicity and lipophilicity. Initial clinical studies with dronedarone did not show significant extracardiovascular toxicity and the ATHENA trial demonstrated a reduction in stroke associated with dronedarone use in AF patients [137]. However, dronedarone is less effective in maintaining sinus rhythm than amiodarone and it is contraindicated in patients with HF [109].

A number of alternative antiarrhythmic strategies for patients with ventricular arrhythmias have been proposed based on preclinical studies. Among these, inhibition of CaMKII, which appears to play a nodal role in both atrial and ventricular arrhythmias, has received significant interest. CaMKII activity is increased in multiple cardiovascular diseases including AF and HF [121], and targets a large number of ion channels and calcium-handling proteins, including L-type calcium channels, RyR2 and phospholamban. Recent studies have highlighted the antiarrhythmic potential of several new CaMKII inhibitors, particularly for conditions in which CaMKII activity is increased. Some of these compounds are currently undergoing clinical testing for rheumatoid arthritis [138], but their antiarrhythmic potential has not yet been evaluated in clinical studies. Alternatively, since RyR2 dysfunction plays a major role in maladaptive cardiac remodeling, e.g., in the setting of HF [139], RyR2 stabilizing

drugs (e.g., K201/JTV-519, S107, carvedilol-analogues), may have a more general therapeutic use, beyond their role in RyR2-associated channelopathies like CPVT.

Atrial specific antiarrhythmic drugs

Despite the rapid development of radiofrequency ablation strategies for the treatment of AF, their effectiveness and safety remain inadequate. Furthermore, these methods can only be applied in a restricted number of patients and therefore pharmacological approaches remain clinically relevant, especially due to the large and growing size of the AF population [109].

The ongoing search for new agents against AF has led to the development of atrial-selective antiarrhythmic approaches [140].

Vernakalant and ranolazine, for example, are the first approaches to selectively target atrial sodium-channels by taking advantage of the biophysical differences between atrial and ventricular channels [141]. In atrial tissue, a higher fraction of sodium channels is in the inactivated state because of the more depolarized resting membrane potential. Since vernakalant and ranolazine bind with higher affinity to activated/inactivated sodium channels than to channels in the closed state, this may contribute to an atrial specific effect on peak sodium current of these drugs [141,142]. In addition, ranolazine predominantly inhibits late sodium current, which is increased in patients with AF and has been suggested to contribute to AF pathophysiology [143,144].

Another approach to developing atrial specific compounds aims to target potassium-channels which are predominantly expressed in the atrium, such as I_{Kur}, $I_{K,ACh}$., two-pore K^+-channels or Ca^{2+}-dependent K^+-channels [145]. Interestingly, some of the already available antiarrhythmic agents, such as flecainide, amiodarone, quinidine, chloroquine or verapamil, inhibit some of these atrial-selective K^+-channels, which may contribute to their antiarrhythmic effect in AF [145].

The unique effectiveness and low arrhythmogenic potential of amiodarone has been attributed, amongst other factors, to its broad spectrum of ion-channel blocking effects [115,145]. Therefore, identification of specific combinations of ion-channel modulating activities could optimize antiarrhythmic efficacy and atrial selectivity. Accordingly, the combination of ranolazine and amiodarone, dronedarone or dofetilide has higher antiarrhythmic efficacy, compared with either drug alone [146,147] and AF-selectivity of sodium channel blockers can be improved by adding potassium channel blockade [148]. In the HARMONY trial the combination of ranolazine and dronedarone showed synergistic effects in reducing AF burden in paroxysmal AF patients [149]. However, at present, currently available evidence is insufficient to recommend antiarrhythmic drug combinations and further research is necessary to define the required channel blocking profile and to validate these approaches in clinical studies.

Basic research during recent years on the mechanisms underlying AF pathology also led to the identification of new potential antiarrhythmic approaches, including the normalization of atrial calcium-handling abnormalities, atrial metabolism or autonomic-tone manipulation. These are currently not implemented in therapeutic strategies and we refer the interested reader to recent reviews [12,115].

Opportunities, challenges and future perspectives

Personalized diagnostic and therapeutic approaches

An increased understanding of patho-mechanisms underlying specific disease subtypes may open the avenue for more specific, personalized therapies. In monogenic channelopathies such as LQTS, for example, this has already led to genotype-specific approaches, e.g. late sodium channel blocker therapy in LQT-3 [27]. However, even mutation-specific, personalized therapies may develop as a) different mutations may convey pronounced differences in arrhythmic risk [32] and b) pronounced mutation-specific differences are observed in response to a given antiarrhythmic drug. The SQTS gain-of-function mutations HERG-N588K and KCNQ1-V307L, for example, alter the extent of I_{Kr}/I_{Ks}-blocking effects of various beta-blocking agents [41] and HERG-N588K may similarly diminish I_{Kr}-blocking (and hence therapeutic) effects of a variety of class I and III agents such as sotalol, quinidine, and amiodarone [150]. Here, the development of patient-specific hiPSC-CM may help to test personalized anti-arrhythmic approaches [151].

Not only in monogenic arrhythmia disorders but also in more common arrhythmias such as AF, a more detailed classification of the disease into "mechanistic" subtypes (see chapter *Mechanism-based stratification of AF subtypes*) may promote patient-oriented rather than generalized therapeutic strategies. miRNAs may help to characterize the substrate or the electrical phenotype in individual AF patients and predict the outcome of interventional therapy [152]. Reduced expression of anti-fibrotic miR29, for example, is associated with increased atrial fibrosis and vulnerability to AF in a canine ventricular tachypacing-induced HF model [153]. Similarly, miR29 expression was reduced in patients with cAF and plasma levels of miR29b could be used to predict the outcome in pAF-patients [154].

Taken together, substratification of AF phenotypes may allow the combination of different mechanism-specific drugs (direct anti-arrhythmic atrial-selective channel-modifying drugs as

well as modifiers of remodeling processes, inflammation etc.) and interventional therapies guided by the disease subtypes [128].

Application of human induced pluripotent stem cell-derived cardiomyocytes in experimental and clinical electrophysiology

Application of hIPSC-CM may theoretically provide the unique opportunity to investigate cardiac electrophysiology of any individual in a non-invasive way and is expected to help closing the gap between experimental and clinical electrophysiology. Ideally, hIPSC-CM could predict arrhythmogenic risk and efficacy of drugs, contributing to personalized medicine. From a broader perspective, studies on cellular electrophysiology would no longer be restricted to tissue harvested during open-heart surgery, allowing intense work on undiseased ventricular tissue. hIPSC-CM should enable repeated investigations, making long and complex functional studies even at different laboratories possible. Classic transgene approaches applied in hIPSC-CM could be used to study heart electrophysiology on a human background. Since hIPSC-CM can be kept in culture over weeks or even months; they could be used to study effects of “long-term” exposure to drugs or increased mechanical load. From this perspective, one could assume that hIPSC-CM could dominate cellular cardiac electrophysiology in the near future; however, there are several critical issue to be addressed.

A central question is how closely hIPSC-CM resemble native human cardiomyocytes, in particular: (1) What type of cardiomyocytes do hIPSC-CM present? Ventricular, atrial, nodal or just a mixture of them [155]? (2) What is the repolarization reserve of hIPSC-CM compared to classic approaches based on animal and undiseased human ventricular tissue [156]? (3) Is the relatively depolarized RMP an intrinsic peculiarity of hIPSC-CM? (4) Are there other reasons for automaticity in hIPSC-CM than low RMP [157]? (5) How to normalize APD when measured at different spontaneous beating rates? Can hIPSC-CM be used as

biological pacemakers [158]? (6) Do hIPSC-CM recapitulate basic findings on cAMP/PKA-mediated contribution to heart pathophysiology? (7) Can hIPSC-CM be used as a model to study human atrial electrophysiology [159]?

To answer these questions, a wide range of cellular electrophysiological techniques is needed. Since it is likely that many of these questions relate to differences in the differentiation and culture of hIPSC-CM, close collaboration between cellular cardiac electrophysiologists and experts in stem cell biology will be mandatory.

Gene- and cell-based therapy

Gene therapy offers greater selectivity than small molecule-based or interventional treatment. The gene of interest is packaged into viral or non-viral carriers and delivered to the target area via direct injection or using catheter-based techniques, providing the advantage of site-restricted action in contrast to systemic application of drugs. Gene therapy for heart rhythm disorders is currently being evaluated in preclinical stages. To date, no antiarrhythmic gene therapy drug is commercially available or has been investigated in clinical trials. Antiarrhythmic effects against AF and ventricular tachycardia, and restoration or suppression of pacemaker activity were successfully achieved in promising pre-clinical gene therapeutic approaches [160]. Cell-based approaches for the treatment of heart rhythm disorders have almost exclusively focused on the generation of biological pacemaker activity [161]. However, in terms of clinical translation most gene and cell therapy strategies are still in early stages of a complex developmental process that involves extensive research and caution prior to widespread human application.

Limitations of the translation of current approaches

One major challenge of efficient translation is the presence of multiple pathophysiological mechanisms in a single disease entity or even an individual patient. Computational

cardiology technologies, comprehensive genetics, or the use of biomarkers may help to overcome this challenge. In addition, the effect of underlying mechanisms on clinical arrhythmia manifestations may vary with time, reducing the potential for the establishment of more generalized treatment recommendations in some cases. Furthermore, experiments using cells derived from animal models and hIPSC-CM do not fully reconstitute phenotypes observed in arrhythmia patients, highlighting the increased need for research employing human cells. In terms of personnel, it is important to recognize that clinical heart rhythm specialists and translational scientists are rarely located in the same unit. In fact, in most cases they do not share the same academic institution or hospital, preventing multidisciplinary exchange, interaction, and collaboration. Other organizational factors pose limitations to translation as well. In clinical electrophysiology departments, the combined workload produced by clinical and scientific work, in addition to administrative duties, writing of grant applications and academic obligations, create an unfavorable environment for focused application of basic findings into optimized patient care. Finally, limited options to obtain substantial funding, particularly for translational electrophysiologists in training, require optimization to promote this emerging field in the long term.

Future perspectives

The ability of an antiarrhythmic intervention to prevent cardiac arrhythmia depends on its capacity to suppress the underlying disease mechanisms. Despite great advances in the mechanistic understanding of inherited channelopathies, translation of mechanism-based novel therapies into clinical use remains challenging due to problems in designing and funding clinical studies with sufficient power in these rare diseases, particularly for "second use" applications of already approved drugs. Additional electrophysiological targets currently in the pipeline include previously unrecognized ion channels, regulatory signaling pathways, structural alterations such as fibrosis that may be targeted by “upstream therapy”, and epigenetic modulation of cardiac electrophysiology. The impact of different comorbidities on

proarrhythmic mechanisms is increasingly recognized as well. Identification of remodeling associated with specific concomitant diseases is expected to enable personalized approaches, for example in patients with AF. It would thus be of great importance to improve funding for translational studies implementing basic science into clinical approaches.

A call to establish and support cellular electrophysiology programs in clinical electrophysiology

Multiple efforts are underway to standardize training and education of heart rhythm specialists in Germany and Europe. At the National level in Germany, a curriculum required to achieve heart rhythm specialist qualification ("Zusatzqualifikation Spezielle Rhythmologie") conveys detailed clinical content on heart rhythm disorders [162]. By contrast, cellular and, particularly, translational electrophysiology is not addressed in detail. Similarly, within the European Core Curriculum for the Heart Rhythm Specialist proposed by the European Heart Rhythm Association [163], training focusses virtually entirely on clinical knowledge and practical skills, and basic science knowledge on arrhythmias is included only to a small extent. However, basic science plays a crucial role in clinical medicine and the health care system by producing novel technologies, drugs, biomarkers, and mechanistic knowledge as basis for patient-oriented therapy that may ultimately serve to save health care budgets by delivering the right therapy to a specific patient. In accordance, the Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM), organized by the European Society of Cardiology and European Heart Academy in collaboration with Maastricht University, explicitly includes sessions on arrhythmia mechanisms and translational electrophysiology.

Despite the recognition and appreciation of translational electrophysiology by European and United States societies for heart rhythm disorders [164,165], a relevant gap is evident between current patient therapy on one side and the implementation of basic research knowledge into clinical decision making on the other. The German Cardiac Society Working Group on Cellular Electrophysiology assumes the responsibility for the promotion of translational electrophysiology within the field of heart rhythm disorders. Therefore, this group of authors proposes the establishment of cellular electrophysiology programs in institutions providing medical care to arrhythmia patients, to optimize patient care through multi-disciplinary diagnostic and therapeutic approaches. In addition, the Working Group

intends to provide a platform for the coordination of nationwide research efforts in the field of translational electrophysiology. This platform is designed to optimize collaborative scientific projects and third-party funded research programs. Furthermore, a “Pathophysiology and Translational Electrophysiology Curriculum” is called for to provide a platform for standardized education of heart rhythm specialists in this hitherto underrepresented field. Ultimately, this educational curriculum may be advanced into a formal “Sachkundekurs: Cellular and Translational Electrophysiology” as part of the “Zusatzqualifikation Spezielle Rhythmologie”. Finally, improved funding for research and education in the field of translational electrophysiology, especially within dedicated translational units, is required to successfully achieve the proposed goals. Anticipated advantages and added value of such infrastructure and programs are summarized in Table 2. A coordinated effort of researchers, translational scientists and clinicians is required to achieve “true” translation and to obtain maximum benefit for optimized therapy of patients affected by heart rhythm disorders.

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Ethical standards

The manuscript does not contain clinical studies or patient data.

Conflicts of interest

D.T. reports receiving lecture fees/honoraria from Bayer Vital, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer Pharma, Sanofi-Aventis, St. Jude Medical and ZOLL CMS, and research grant support from Daiichi Sankyo. A.G. reports speaker fees from Astra Zeneca, Berlin Chemie, Biotronik, Boehringer Ingelheim, Bayer Health Care, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Medtronic. M.H. reports speaker fees from Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Bayer Health Care, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo. D.L. reports serving on the advisory board of LivaNova and Medtronic, receiving lecture fees/honoraria from LivaNova, Medtronic, Pfizer and ResMed, and receiving research grant support from Sanofi, ResMed and Medtronic. J.H. reports speaker fees from Pfizer. N.V. reports receiving research suppor from Nissan Biochemical.

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Tables

Table 1. VT in ischemic cardiomyopathy: a systematic analysis of significant mRNA level alterations (transcriptomics) of the infarction border zone may provide novel antiarrhythmic drug targets. For further information see text (Modified after [96])

Process	Gene	Averaged transcript level fold change (BZ-D vs. BZ)
Death of Cardiomyocytes	PSRC1	6.06
	NDFIP1	6.05
	LAMP2	3.10
Acute Inflammation	CXCL6	9.23
	IL6	8.18
	IL23R	8.08
	HCK	7.54
	CXCL9	5.27
Regression of Inflammatory Signaling	THBS1	3.64
	TNFAIP6	3.39
Stimulation of Extracellular Matrix by Cardiac Fibroblasts	ITGA8	5.04
	SMURF1	2.84
	TIMP1	2.14
	THBS2	2.09
Formation of Mature Scar	COL8A1	5.1
	FN1	4.46
	TNN	3.93
	TNC	7.77
	STAT3	3.64
	GPNMB	3.49
	LMNA	3.48
	POSTN	3.38
	ACAN	2.85
	COL1A2	2.43
	VCAN	2.41
	CTGF	2.32
	COMP	2.30

Table 2. Benefits of dedicated cellular electrophysiology programs associated with clinical electrophysiology departments

Patient care and translation	Ready translation of basic scientific findings into clinical application and improved patient diagnosis and treatment.
Basic science and "reverse" translation	Clinical findings and challenges trigger and guide scientific hypotheses and approaches.
Education	Training of "translational electrophysiologist" physician scientists [165,166] who display both basic science expertise and specialized clinical knowledge in heart rhythm disorders.
Infrastructure	Creation of an environment that allows for a combined scientific and clinical approach to specific challenges in the understanding and management of arrhythmias.
Network	Implementation of a "German Cardiac Society Working Group on Cardiac Cellular Electrophysiology Network for Translational Research" provides a platform for nationwide interdisciplinary research and application.
Funding	Generation of optimized prerequisites for successful acquisition of funding for research efforts.

Figures

Figure 1: Cellular mechanisms underlying ectopic activity. A, Abnormal automaticity is caused by spontaneous diastolic depolarization to a threshold value for activation. **B, C** Abnormal membrane depolarizations preceding full repolarization (**B,** early afterdepolarizations [EADs]) or after completion of the action potential (**C,** delayed afterdepolarizations [DADs]) or repolarization (early afterdepolarizations [EADs]) may also cause spontaneous activity. (Replotted with kind permission from [167])

Figure 2: Current concepts of functional reentry. A, The leading circle concepts is based on a reentering excitation travelling around a functional refractory and therefore unexcitable core. The circuit size is determined by the wavelength i.e. the distance travelled by the cardiac impulse in one effective refractory period (ERP), given by the product of conduction velocity (CV) and ERP. **B,** In the spiral wave concept reentry occurs around an excitable but continuously unexcited corecore and maintenance depends on balance of current-source/tissue-excitability (favoring propagation) and current-sink (impairing propagation). (Adapted with kind permission from [9])